PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/008190	22.07.2004	22.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61P37/04, A61K39/39, A61K9/127

Applicant
CYTOS BIOTECHNOLOGY AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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10/565264

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/008190

IAP20 Rec'd PCT/PTO 20 JAN 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-17,20-21 (IA)

because:

☒ the said international application, or the said claims Nos. 15-17, 20-21 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12
	No:	Claims	1-11, 13-22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-14, 18-19,22
	No:	Claims	

2. Citations and explanations

see separate sheet

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Item III

III.1 With respect to claims 15-17, 20, and 21

Claims 15-17, 20, and 21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Item V

V.1 Reference is made to following documents

D1: US2003/0060440 (D. KLINMAN ET AL.) 27 March 2003 (2003-03-27)
D2: US2003/0087848 (R.L. BRATZLER ET AL.) 08 May 2003 (2003-05-08)
D3: US2003/0050268 (A.M. KRIEG & D.J. BERG) 13 March 2003 (2003-03-13)
D4: WO2003/045431 (SCHERING CORPORATION) 05 June 2003 (2003-06-05)
D5: WO2003/030656 (MERIAL LIMITED & UNIVERSITY OF SASKATCHEWAN) 17 April 2003 (2003-04-17)
D6: WO2003/024481 (CYTOS BIOTECHNOLOGY) 27 March 2003 (2003-03-27)
D7: WO2004/000351 (CYTOS BIOTECHNOLOGY) 31 December 2003 (2003-12-31)

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims

Document D1 describes A-type (D-type) CpGs comprised in a delivery complex being amongst others a liposome composed of cationic lipids (paragraph [0013], [0105]-[0113], [0138]). Said CpG molecules comprise a palindromic sequence [0116]. Said liposome-CpG composition is administered i.v., i.m, or i.p. (paragraph [0140]). A A-type CpG is described by the formula 5' RY-CpG-RY, wherein R is A or G and Y is C or T (paragraph [106]-[107]). The liposome-CpG composition is used for the treatment of cancer and infectious diseases (paragraph [0154]-[0156]).

Document D2 describes the CpG oligonucleotides referred to as SEQ ID NO. 959, 1071, and 1075 (Table 1 p. 18 and p. 20), being ggggacgatcgtcggggg, gggacgatcgtcgggggg, and ggggacgatcgtcgggggg (20 nucleotides), comprising a

chimeric combination of phosphodiester and phosphorothioate (paragraph [0073]) (emphasis added, underlined sequence is the palindromic sequences as referred to SEQ ID NO. 16 of the present application). A vector for delivering the CpG oligonucleotides being liposomes is described (paragraph [0147]-[0150]). Said oligonucleotides may be used for the treatment of bacterial or viral infections (paragraph [0169]). The composition may be administered e.g. orally, i.p., or I. m. (paragraph [0188]).

Document D3 describes the CpG oligonucleotides referred to as SEQ ID NO. 917, 950, 951, 1015, 1019 (Table 1 p. 34 and p. 36), being ggggg<u>acgatcgtcg</u>gggg, gggggg<u>acgatcgtcg</u>gggggg (21 nucleotides), gggggacgatcgtcgggggggg (21 nucleotides), gggacgatcgtcgggggggg, ggggacgatcgtcgggggggg (20 nucleotides) comprising a chimeric combination of phosphodiester and phosphorothioate with phosphorothioate at the 5' and 3' ends (paragraph [0098]) (emphasis added, underlined sequence is the palindromic sequences as referred to SEQ ID NO. 16 of the present application). The sequences as referred to SEQ ID NO. 950, 951 and 1015 are preferred oligonucleotides inducing IFN type I (IFN alpha and beta) (paragraph [0115] and Table 2). The oligonucleotide molecules are in the range of 6 to 100 bases in length (paragraph [0133]). The composition comprising the CpG oligonucleotides may be delivered in association with a vector being e.g. a liposome (paragraph [0150], [0158]-[0161]). Said composition may be administered e.g. orally, i.v., i.m. and may be used for the treatment of non-allergic inflammatory diseases, e.g. psoriasis (paragraph [0044]).

Document D4 describes the oligonucleotide designated CpG 2216, which is an A-type CpG with the sequence gggggacgatcgtcgggggg (20 nucleotides) (p 16 Table 2, claim 12) and may be administered by injection (i.v. or i.m.) (p. 17 l. 26-28). The CpG oligonucleotide is encapsulated in cationic liposomes (p. 15 l. 25-31, claim 14).

Document D5 describes the CpG oligonucleotide ggGG<u>GACGATCGTC</u>ggggG (20 nucleotides) (lower case Gs represent residues that are linked together by phosphorothioate linkages while upper case Gs represent residues that are linked together by phosphodiester linkages (p. 4 l. 3-8, p. 23 l. 22-27). Said CpG oligonucleotide is administered in a lipid based delivery system in an animal feed (p. 7 l. 16-19), but may be also delivered parenterally, e.g. s.c. (p. 16 l. 29-31 and p. 17 l. 21-24) in a liposome of cationic lipids (p. 33 l. 30 - p. 34 l. 1, p. 37 l. 4-7). Said

CpGs are administered in the absence of an antigen (p. 22 l. 9-12) for the induction of IFN alpha which is effective in the treatment of microbial infections (p. 18 l. 11-25).

In the light of D1-D5, the subject-matter of claims 1-11, and 13-22 is not considered novel in the sense of Article 33(2) PCT.

V.2.2 With respect to claim 12

None of the documents above disclose the subject-matter of claim 12, i.e. the CpG oligonucleotide as referred to SEQ ID NO. 3 in combination with a liposome (for the definition of the term "bound" see p. 8 l. 24 - p. 9 l. 5 of the present application). Therefore, the subject-matter of claim 12 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claim 12

The subject-matter of claim 12 differs from the closest prior art documents D2-D5 in that the number of G residues at both of the 5' and 3' end is 10 instead of 3/5, 2/7, 3/7 (D2), 4/5, 5/6, 4/7, 2/7, 3/7 (D3), 4/6 (D4 and D5). The technical problem to be solved my be formulated as providing an alternative CPG-liposome composition comprising an alternative CpG oligonucleotide. The CpG oligonucleotide G10-PO as referred to SEQ ID NO. 3 is known from D6 (p. 110 Table I) in which said oligonucleotide is packaged into VLPs and is further used for the treatment of infectious diseases. The solution proposed in present claim 12, i.e., to use the known CpG oligonucleotide in combination with a liposome, appears to be obvious to the skilled person. Therefore, the subject-matter of claim 12 is not considered inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-14, 18, 19, and 22

The subject-matter of claims 1-14, 18, 19, and 22 appears to be susceptible of industrial application.

V.4.2 With respect to claims 15-17, 20, and 21

The subject-matter of claims 15-17, 20, and 21 is considered to be a method of

treatment by therapy of the human or animal body.

For the assessment of the present claims 15-17, 20, and 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI

VI.1 With respect to document D7

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited documents D7 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT).